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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/599,877	06/23/2000	Johan Lennerstrand	07691.0004	1424

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EXAMINER	
PARKIN, JEFFREY S	

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 08/26/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/599,877	LENNERSTRAND ET AL.	
	Examiner	Art Unit	
	Jeffrey S. Parkin, Ph.D.	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *03* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 May 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14,20 and 21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14,20 and 21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Detailed Office Action

37 C.F.R. § 1.114

A request for continued examination under 37 C.F.R. § 1.114, including the fee set forth in 37 C.F.R. § 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 C.F.R. § 1.114, and the fee set forth in 37 C.F.R. § 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 C.F.R. § 1.114. Applicants' submission filed on 03 May, 2004, has been entered.

Status of the Claims

Claims 1-14, 20, and 21 are currently under examination.

35 U.S.C. § 112, Second Paragraph

Claims 1-14, 20, and 21 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 20, and 21 all include the phrase "**the reaction products of substances**" which remains vague and indefinite. Applicants response failed to address this deficiency. This phrase is confusing since the skilled artisan would first add assay **reagents** (**not reaction products**) to the reaction well, followed by the enzyme of interest. The resultant extension products arising from the activity of the enzyme could then be assayed using a number of standard formats (i.e., TCA precipitation). Appropriate correction is required (i.e., providing a reaction well with the following assay components: i) at least one template for an HIV RT enzyme ...; providing a reaction well with the following assay

reagents: i) at least one template for an HIV RT enzyme ...). Applicants are again directed toward pages 23 and 24 of the disclosure for suggestions in drafting appropriate claim language.

Claims 1, 20, and 21 are further rejected under 35 U.S.C. § 112, second paragraph, because the reference to various RT mutations (e.g., M41L) is vague and indefinite. First the term HIV encompasses both HIV-1 and -2. However, these viruses only share limited genetic relatedness. Accordingly, the numbering scheme will differ considerably from HIV-1. Thus, it is not readily manifest if the reference to M41L references an HIV-1 or -2 isolated. Second, when referencing various RT mutations in the claims, an art-recognized reference isolate should also be included. Since the human immunodeficiency viruses exist as a quasispecies, there is genetic variation even within the same patient. However, by providing a reference isolate it will enable the skilled artisan to accurately determine where the precise mutation is in any given enzyme (i.e., wherein said mutant is selected from the group consisting of M41L/T215Y...wherein said numbering scheme is based upon the prototypical isolate HIV-1_{BH-10}).

Claim 13 references a mutant containing mutations at codons 67, 69, and 70. However, the parent claim fails to mention this combination of mutations. Accordingly, there is insufficient antecedent basis for this limitation in the claim.

Claim 14 remains rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants' response failed to address this concern. The claims still reference an "insertional mutation at nucleotide triplet encoding codon 69" which is vague and indefinite since the precise nature and location of the mutation is not clearly set forth. Perusal of the disclosure indicates the drug-

resistant forms of RT contain a single or multiple amino acid insertion between codons 69 and 70. Appropriate amendment of the claim language is required (i.e., wherein the HIV-1 mutant RT enzyme contains **an amino acid insertion between codons 69 and 70**).

35 U.S.C. § 103(a)

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. § 103© and potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103(a).

The factual inquiries set forth in *Graham et al. v. John Deere Company of Kansas City et al.; Calmar, Inc. v. Cook Chemical*

Company; Colgate-Palmolive Company v. Same, 148 U.S.P.Q. 459 (U.S. Sup. Ct. 1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103 are summarized as follows: 1) Determining the scope and contents of the prior art. 2) Ascertaining the differences between the prior art and the claims at issue. 3) Resolving the level of ordinary skill in the pertinent art. 4) Considering objective evidence present in the application indicating obviousness or unobviousness.

Claims 1-3, 5-12, 20, and 21 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Meyer *et al.* (1999) in view of Ekstrand *et al.* (1996) and Kellam *et al.* (1992). The claims are directed toward an HIV RT assay to assess the resistance of any given RT sample to treatment with an HIV RT inhibitor. The claims require a reaction well with the following components: (i) at least one template for an HIV RT enzyme; (ii) at least one primer; (iii) at least one detectable dNTP substrate; (iv) at least one HIV RT inhibitor; and (v) at least one ribonucleotide chosen from ATP and GTP, or at least one pyrophosphate. Additional steps recite comparative steps involving both the wildtype and mutant RTs.

Meyer *et al.* (1999) provide an HIV RT enzymatic assay to examine mutant activity that employs at least one template, at least one primer, at least one RT inhibitor, and either ATP/GTP or pyrophosphate (see Experimental Procedures, p. 42). The authors reported (p. 35, rt. col.) that "we describe an *in vitro* assay that reproduces the essential *in vivo* properties of the AZT resistance mutants. HIV-1 RT containing the D67N, K70R, T215F, and K219Q amino acid substitutions (designated as 67/70/215/219 RT in this report) was much more efficient than WT RT at extending the primer past several potential termination sites in the presence of AZTTP when ATP was added to the reaction. Transfer of the AZTMP residue from the primer terminus to ATP to form dinucleoside polyphosphate

and unblocked primer was enhanced in the 67/70/215/219 RT."

The authors also noted (see p. 35, last paragraph, rt. col.) that the "Addition of a ribonucleoside triphosphate (ATP) to the reaction mixture provided an acceptor for the nucleotide-dependent primer unblocking activity in which the AZTMP residue from the chain-terminated primer was transferred to ATP to form Ap_4AZT, and the primer was shortened by one residue and was no longer blocked to elongation". The authors finally conclude (see p. 36, rt. col.) that "by adding ATP at concentrations likely to be present in intact cells, we have established an in vitro system that reflects the in vivo properties of the 67/70/215/219 mutant virus." The only limitations of this teaching is that it does not disclose an RT assay that employs a detectable dNTP and a mutant RT having the claimed mutations.

Ekstrand *et al.* (1996) provide a non-radioactive reverse transcriptase assay that employs 5-bromodeoxyuridine 5'-triphosphate (BrdUTP) as the detectable dNTP (see Materials and Methods, p. 97). The assay described employs an alkaline phosphatase-conjugated anti-BrdU antibody and provides quantitative results. The authors note (see p. 104, last paragraph) "the present paper describes a simple, sensitive and non-radioactive RT assay with kinetic features similar to those observed when the natural dTTP substrate is used." This teaching does not disclose the utilization of HIV-1 RT mutants having the claimed mutations.

Kellam *et al.* (1992) identified mutant HIV-1 RTs that played a role in drug-resistance. Specifically, mutant RTs carrying the mutations M41L and T215Y were identified and their enzymatic activity ascertained (see Table 2, p. 1937).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to utilize the detection format described by Ekstrand *et al.* (1996), in the RT assay provided by Meyer *et al.* (1999), since this

provides a rapid, quantitative, and non-radioactive means for detecting the products of reverse transcription. Moreover, it would have also been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to employ the mutant RTs disclosed by Kellam *et al.* (1992) since these represent clinically important variants.

1. Applicants previously provided a declaration by Dr. Jochmans pursuant to 37 C.F.R. § 1.132 asserting that the claimed invention is unobvious in view of the prior art. The crux of the invention appears to be related to the use of a ribonucleotide (i.e., one of ATP or GTP) in the RT reaction mixture to facilitate the detection of drug-resistant variant RTs. The inclusion of a ribonucleotide apparently results in a more sensitive assay because it removes the block in polymerization stemming from the RT inhibitor. This is precisely the same format employed in the assay described by Meyer *et al.* (1999). In fact, Meyer and colleagues clearly stated that the inclusion of a ribonucleotide relieved the block in polymerization. Thus, contrary to the assertions of the declarant, the prior art appears to provide the crux of the claimed invention.

It was further argued in the declaration that the prior art fails to teach the detection of multiple chain termination events in a single well. This is precisely what Meyer and colleagues disclose. The inclusion of the ribonucleotide relieves the block in polymerization thereby enabling one of ordinary skill in the art to detect multiple chain termination events by the mutant RT in the reaction well. The reaction conditions described by Meyer *et al.* (1999) are nearly identical to those described and claimed by applicants. The only deficiency in this teaching is its failure to describe the utilization of a labeled dNTP, such as BrdUTP. However, Ekstrand *et al.* (1996) provide a suitable label. Moreover, there was sufficient motivation to utilize this label in

the assay of Meyer *et al.* (1999) and a reasonable expectation that the modified assay would be successful. Thus, the declarant's argument concerning this point is not persuasive.

Applicants have previously argued that sufficient motivation and a reasonable expectation of success were not present in the prior art. These arguments were clearly not persuasive in view of the prior art. Moreover, as previously set forth, the Examiner recognizes that references cannot be arbitrarily combined and that there must be some reason why one skilled in the art would be motivated to make the proposed combination of primary and secondary references. *In re Nomiya*, 184 U.S.P.Q. 607 (C.C.P.A. 1975). However, there is no requirement that a motivation to make the modification be expressly articulated. The test for combining references is what the combination of disclosures taken as a whole would suggest to one of ordinary skill in the art. *In re McLaughlin*, 170 U.S.P.Q. 209 (C.C.P.A. 1971). References are evaluated by what they suggest to one versed in the art, rather than by their specific disclosures. *In re Bozek*, 163 U.S.P.Q. 545 (C.C.P.A. 1969). As set forth *supra*, both the motivation and a reasonable expectation of success were present in the prior art. One of ordinary skill in the art would have had sufficient motivation to utilize the detection format described by Ekstrand *et al.* (1996), in the RT assay provided by Meyer *et al.* (1999), since this would provide a rapid, quantitative, and non-radioactive means for detecting the products of reverse transcription.

Claim 4 is rejected under 35 U.S.C. § 103(a) as being unpatentable over Meyer *et al.* (1999) in view of Ueno *et al.* (1995) and Kellam *et al.* (1992). The content of Meyer *et al.* (1999) and Kellam *et al.* (1992) is disclosed in the preceding paragraph. Meyer and colleagues do not describe the utilization of an art-recognized RT activity label such as a radioactive dNTP, although a

labeled primer was employed. However, Ueno *et al.* (1995) describe standard HIV RT assays that employ art-recognized labels such as radioactive labeled dNTPs (see pp. 23605-23606, EXPERIMENTAL PROCEDURES, *Materials* and *Product Analysis*). Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to utilize a radiolabeled dNTP, as taught by Ueno *et al.* (1995), in the assay of Meyer *et al.* (1999), since this represents a standard and art-recognized means for detecting RT reaction products. Moreover, it would have also been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to employ the mutant RTs disclosed by Kellam *et al.* (1992) since these represent clinically important variants.

Claims 13 and 14 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Meyer *et al.* (1999) in view of Ekstrand *et al.* (1996), as applied *supra* to claims 1-3, 5-12, 20, and 21, and further in view of Larder *et al.* (1999a, 1999b). The combination of references employed *supra* do not disclose the use of HIV RT mutants carrying mutations at amino acid positions 67, 69, and 70, or an insertion between amino acids 69 and 70. However, both Larder *et al.* (1999a, 1999b) publications disclose that HIV-1 RT resistant variants, particularly MNR variants, carry mutations at amino acids 67, 69, and 70, and between amino acids 69 and 70. Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to utilize the HIV-1 RT mutants described by Larder *et al.* (1999a, 1999b), in the reverse transcriptase assay suggested by Ekstrand *et al.* (1996) and Meyer *et al.* (1999). One of ordinary skill in the art would have been motivated to include these mutant forms of the RT since they naturally develop during the course of antiviral therapy. Applicants' arguments are not convincing for the reasons

of record set forth *supra*.

Claims 1-3, 5-12, 20, and 21 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Arion *et al.* (1998) in view of Ekstrand *et al.* (1996) and Kellam *et al.* (1992). Arion *et al.* (1999) provides an HIV RT enzymatic assay to examine mutant activity that employs a template, primer, RT inhibitor, and pyrophosphate (see p. 15910, MATERIALS AND METHODS, *Analysis of Chain Termination of RT-Catalyzed DNA Synthesis*). The authors suggested (see p. 15908, ABSTRACT) that "HIV-1 resistance to AZT results from the selectively decreased binding of AZTTP and the increased pyrophosphorolytic cleavage of chain-terminated viral DNA by the mutant RT at physiological pyrophosphate levels, resulting in a net decrease in chain termination. The increased processivity of viral DNA synthesis may be important to enable facile HIV replication in the presence of AZT, by compensating for the increased reverse reaction rate." This teaching does not disclose an RT assay that employs a detectable dNTP or an RT mutant having the claimed mutations.

However, Ekstrand *et al.* (1996) provide a non-radioactive reverse transcriptase assay that employs 5-bromodeoxyuridine 5'-triphosphate (BrdUTP) as the detectable dNTP (see Materials and Methods, p. 97). The assay described employs an alkaline phosphatase-conjugated anti-BrdU antibody and provides quantitative results. The authors note (see p. 104, last paragraph) "the present paper describes a simple, sensitive and non-radioactive RT assay with kinetic features similar to those observed when the natural dTTP substrate is used." This teaching also fails to disclose the use of an RT enzyme having the recited mutations.

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to utilize the detection format described by Ekstrand *et al.* (1996),

in the RT assay provided by Arion *et al.* (1998), since this provides a rapid, quantitative, and non-radioactive means for detecting the products of reverse transcription. Moreover, it would have also been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to employ the mutant RTs disclosed by Kellam *et al.* (1992) since these represent clinically important variants.

Applicants' arguments set forth in the declaration of Dr. Jochmans were addressed above. Applicants previously argued that both sufficient motivation and a reasonable expectation of success were not present in the prior art is not convincing. These arguments are clearly not persuasive in view of the prior art and knowledge of the skilled artisan. Moreover, the Examiner recognizes that references cannot be arbitrarily combined and that there must be some reason why one skilled in the art would be motivated to make the proposed combination of primary and secondary references. *In re Nomiya*, 184 U.S.P.Q. 607 (C.C.P.A. 1975). However, there is no requirement that a motivation to make the modification be expressly articulated. The test for combining references is what the combination of disclosures taken as a whole would suggest to one of ordinary skill in the art. *In re McLaughlin*, 170 U.S.P.Q. 209 (C.C.P.A. 1971). References are evaluated by what they suggest to one versed in the art, rather than by their specific disclosures. *In re Bozek*, 163 U.S.P.Q. 545 (C.C.P.A. 1969). As set forth supra, both the motivation and a reasonable expectation of success were present in the prior art. One of ordinary skill in the art would have had sufficient motivation to utilize the detection format described by Ekstrand *et al.* (1996), in the RT assay provided by Arion *et al.* (1998), since this provides a rapid, quantitative, and non-radioactive means for detecting the products of reverse transcription.

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Claims 13 and 14 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Arion *et al.* (1998) in view of Ekstrand *et al.* (1996) and Kellam *et al.* (1992) as applied *supra* to claims 1-3, 5-12, 20, and 21, and further in view of Larder *et al.* (1999a, 1999b). The combination of references employed *supra* do not disclose the use of HIV RT mutants carrying mutations at amino acid positions 67, 69, and 70, or an insertion between amino acids 69 and 70. However, both Larder *et al.* (1999a, 1999b) publications disclose that HIV-1 RT resistant variants, particularly MNR variants, carry mutations at amino acids 67, 69, and 70, and between amino acids 69 and 70. Therefore, it would have been *prima*

facie obvious to one having ordinary skill in the art at the time the invention was made to utilize the HIV-1 RT mutants described by Larder *et al.* (1999a, 1999b), in the reverse transcriptase assay suggested by Ekstrand *et al.* (1996) and Arion *et al.* (1998). One of ordinary skill in the art would have been motivated to include these mutant forms of the RT since they naturally develop during the course of antiviral therapy. Applicants' arguments are not convincing for the reasons of record set forth *supra*.

Correspondence

Any inquiry concerning this communication should be directed to Jeffrey S. Parkin, Ph.D., whose telephone number is (571) 272-0908. The examiner can normally be reached Monday through Thursday from 9:30 AM to 7:00 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner are unsuccessful, the examiner's supervisors, Laurie Scheiner or James Housel, can be reached at (571) 272-0910 or (571) 272-0902, respectively. Direct general inquiries to the Technology Center 1600 receptionist at (571) 272-1600. Formal communications may be submitted through the official facsimile number which is (703) 872-9306. Hand-carried formal communications should be directed toward the customer window located in Crystal Plaza Two, 2011 South Clark Place, Arlington, VA. Applicants are directed toward the O.G. Notice for further guidance. 1280 O.G. 681. Informal communications may be submitted to the Examiner's RightFAX account at (571) 273-0908.

Respectfully,

Jeffrey S. Parkin, Ph.D.
Patent Examiner
Art Unit 1648

22 August, 2004